

**Medtronic**

Medtronic, Inc.
710 Medtronic Parkway NE
Minneapolis, MN 55432-5604 USA
www.medtronic.com

7635055000

December 3, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. 2004D - 0431 - Guidance for Industry and FDA, Current Good
Manufacturing Practice for Combination Products**

Dear Sir or Madam:

Medtronic Neurological, a division of Medtronic, Inc., is engaged in the research, development and marketing of restorative neuroscience products and therapies through site specific controlled delivery of electrical stimulation, drugs and biologics to the central and peripheral nervous system. Our marketed products include implantable infusion systems and other drug delivery devices. We also develop pharmaceuticals and biologics to be used in conjunction with delivery devices.

Medtronic Vascular designs and markets technologies for coronary, endovascular, and peripheral vascular indications. Products include stents, stent grafts, balloon angioplasty catheters, guide catheters, and guidewires. Drug-eluting stents are currently in development.

Both Medtronic divisions have combination products as defined in 21 CFR 3.2(e).
Medtronic Neurological's combination products are covered by 21 CFR 3.2(e)(3)¹ while

¹ 21 CFR 3.2 (e) (3) - A drug, device or biological product packaged separately that according to is investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose;,,,

2004D-0431*When Life Depends on Medical Technology***C7**

Medtronic Vascular's product is a single-entity combination product as defined in 21 CFR 3.2(e)(1)². The comments that follow are the combined comments of Medtronic Neurological and Medtronic Vascular.

GENERAL COMMENTS

Medtronic supports the principles behind the draft guidance and applauds the Agency in issuing this draft guidance for combination products. This GMP guidance is constructive and represents a well-balanced view of a difficult topic. We respectfully submit the following comments for FDA's consideration.

Section III.A. – Background

The draft guidance acknowledges that the Quality System (QS) and Current Good Manufacturing Practice (CGMP) regulations overlap considerably in content and intent. Both regulations allow flexibility in application of requirement to the manufacture of specific products. Medtronic believes that these facts support flexible application of a single quality system to combination products.

Section III.B. – Current Good Manufacturing Practice for Combination Products

We appreciate FDA's acknowledgement that many manufacturing facilities operate under one type of quality system (current good manufacturing practice system) and that compliance with both sets of regulations can be "generally be achieved by using either the CGMP or QS regulations".

A Single Quality System Approach

Medtronic agrees that adaptation of a single quality system can assure compliance with with the applicable requirements of both sets of regulations (QS and CGMP) -- particularly with convergence of QS and CGMP concepts apparent in the draft guidance

² 21 CFR 3.2(e)(1) – A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

on the quality system approach to pharmaceutical CGMP³. However, some statements in the draft guidance on CGMP for combination products, if interpreted independently, imply a more restrictive approach (i.e. that all requirements of the QS and CGMP regulations are applicable to certain products), and may even have contradictory requirements. Specific suggestions for re-wording these statements are provided later in these comments.

We urge FDA to exercise flexibility in allowing application of the predominant quality system of the facility to combination products. Not all of the specific requirements stipulated in the CGMP or QS regulations would apply to a combination product regulated as a device and under the primary jurisdiction of CDRH. FDA already has some good examples listed in Table 1 of the DRAFT GUIDANCE. Requirements such as yield calculations, stability testing, reserve samples, final product testing and release for distribution, etc. may not apply to all combination products in all cases.

Early Consultation with FDA

Medtronic agrees that early consultations between the sponsor and various stakeholders within FDA would be useful.

Training of Compliance Personnel

In addition, we recommend that FDA provide training for compliance staff (field and headquarters personnel) to ensure flexibility in interpreting these requirements and in exercising compliance discretion when inspecting manufacturers of combination products.

³ DRAFT GUIDANCE – Guidance for Industry – Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2004, US HHS, FDA, CDER, CBER, CVM and ORA.

Consideration of Issuance of Compliance Policy Guide for Combination Products

In order to provide training and avoid inconsistencies in interpretations and enforcement of good manufacturing requirements by field personnel, Medtronic proposes that the Agency draft a Compliance Policy Guide (CPG) specifically for Combination Products, provide the opportunities for stakeholders to comment, and use this CPG for training purposes. The Agency may look to the excellent precedent set by CDRH when transitioning device GMP inspections to the Quality System Inspection Technique (QSIT).

The compliance policy guide may contain a detailed "mapping" of every section of the CGMP with QS regulations, to provide clarity and specificity to compliance personnel. Stakeholders such as industry associations and professional associations may provide input to the Agency.

SPECIFIC COMMENTS

Center Interaction

Page 3, lines 82-84

Change from: "The lead center generally has responsibility for oversight of the regulation of the combination product, including the evaluation of current good manufacturing practice."

Change to: "The lead center generally has responsibility for oversight of the regulation of the combination product, including the evaluation of current good manufacturing practice, but may request consultative advice from additional agency Centers as appropriate."

Predominant Quality System Approach

Page 5, lines 159-161

Change from: "However, for combination products that are produced as a single-entity or are co-packaged, see 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together."

Change to: "However, for combination products that are produced as a single-entity or are co-packaged, a primary set of current good manufacturing practices is applicable. During and after joining the constituent parts together, the primary set of regulations may be supported by specific requirements from the other set. The predominant quality system of the manufacturing facility should serve as the primary set of regulations."

Page 5, Lines 176-179

Change from: "During and after joining these types of combination products together, FDA believes that compliance with both sets of regulations can generally be achieved by following one set because under a more general requirement in one set of regulations, it will be possible to develop and implement a practice that complies with a more specific requirement in the other set of regulations."

Change to: "During and after joining these types of combination products together, FDA believes that compliance with both sets of regulations can be generally achieved by following the predominant quality system of the manufacturing facility supplemented by specific requirements of the other regulation. This approach is appropriate because under a more general requirement in one set of regulations, it will be possible to develop and implement a practice that complies with a more specific requirement in the other set of regulations."

Page 6, Lines 188-189

Change from: ".....carefully consider these provisions during and after joining the constituent parts, to ensure compliance with both the CGMP and QS regulations."

Change to: ".....carefully consider these provisions during and after joining the constituent part, to ensure compliance with the primary set of regulations and specific requirements of the other set of regulations. The specific CGMP or QS requirements outlined in Table 1 that are not considered partly or completely applicable to the combination product should be appropriately justified. Practical considerations and the principles of risk management should be evaluated in the approach to these requirements."

Page 7, lines 235-236

Change from: "Once the product is combined into a single entity or co-packaged, both sets of regulations apply to the combination."

Change to: "Once the product is combined into a single entity or co-packaged, the predominant quality system in the manufacturing facility would apply, supplemented as necessary by specific requirements of the other set of regulations."

Thank you for providing the opportunity to comment on this guidance.

Sincerely,



Winifred C. Wu, RPh
Senior Regulatory Director
Medtronic Neurological



Diana K. Salditt
Senior Manager
Medtronic Corporate Regulatory Affairs